

REMARKS

Claims 38 to 43 are pending in the present application. In view of the following remarks, applicants respectfully request reconsideration and withdrawal of the rejections and objections set forth in the Office Action.

Claim Rejections - 35 U.S.C. §103

In the Office Action claims 38 to 43 were "rejected under 35 U.S.C. § 103(a) as being unpatentable over Himmelsbach, et al. in US 6,924,285" because

a) Himmelsbach teaches 4-(3-chloro-4-fluoroanilino)-7-methoxy-6-{{[1-(N-methylcarbamoylmethyl)piperidin-4-yl]oxy}quinazoline, where p-F is bonded to the anilino ring at C-4 of the quinazoline core; b) Himmelsbach teaches that 4-(3-chloro-4-fluoroanilino)-7-methoxy-6-{{[1-(N-methylcarbamoylmethyl)piperidin-4-yl]oxy}quinazoline and 4-(3-chloro-2-fluoroanilino)-7-methoxy-6-{{[1-(N-methylcarbamoylmethyl)piperidin-4-yl]oxy}quinazoline are alternatively usable; and c) the courts have recognized that *structural similarity between claimed and prior art subject matter, proved by combining references or otherwise, where the prior art gives reason or motivation to make the claimed compositions or compounds, creates a prima facie case of obviousness*, one having ordinary skill in the art, at the time this invention was made, would have been motivated to utilize the teachings of Himmelsbach and replace the p-F of the anilino ring at C-4 of the quinazoline core in Himmelsbach's 4-(3-chloro-4-fluoroanilino)-7-methoxy-6-{{[1-(N-methylcarbamoylmethyl)piperidin-4-yl]oxy}quinazoline with an alternatively usable o-F, and formulate a pharmaceutically acceptable salt or pharmaceutical composition thereof, with a reasonable expectation of success and similar therapeutic activity, rendering claims 38-43 obvious.

Applicants respectfully disagree and traverse this rejection.

For chemical compounds

[p]roof of obviousness based on structural similarity requires... evidence that a medicinal chemist of ordinary skill would have been motivated [1] to select and then [2] to modify a prior art compound (e.g., a lead compound) to arrive at a claimed compound with a reasonable expectation that the new compound would have similar or improved properties compared with the old.

Daiichi Sankyo Co., Ltd. v. Matrix Laboratories, Ltd., 619 F.3d 1326, 1352 (Fed. Cir. 2010) (citations omitted)

In the present case, applicants respectfully submit that one of ordinary skill in the art would not have had any reason to select 4-(3-chloro-4-fluoroanilino)-7-methoxy-6-{{[1-(N-methylcarbamoylmethyl)piperidin-4-yl]oxy}quinazoline, Example (38) in column 69, from Himmelsbach as a lead over better-studied compounds. Applicants further

submit that one of ordinary skill in the art would not have had a reason to make the proposed modification of Example (38) in light of the existence of numerous possible modifications, the fact that the proposed modification would have resulted in rejecting the clearly preferred substitution (3-, 4-, or 3,4-) of the phenyl group of Himmelsbach's compounds, and the fact that Himmelsbach fails to disclose a single compound having any substitution at the ortho (or 2-) position.

I. Selection of a Lead Compound

First, an "obviousness argument based on structural similarity between claimed and prior art compounds 'clearly depends on a preliminary finding that one of ordinary skill in the art would have selected [the compound] as a lead compound.'" Procter & Gamble Co. v. Teva Pharmaceuticals USA, Inc., 566 F.3d 989, 994 (Fed. Cir. 2009)(internal citation omitted). However, the present Office Action does not contain any preliminary finding why one of ordinary skill in the art would have selected Example (38) as a lead.

Rather, Example (38) from Himmelsbach appears to have been chosen as a lead merely because it is the structurally closest compound in the art. However, selecting a lead solely based on structural similarity "runs contrary to our case law. In *Takeda*, [the Federal Circuit] upheld a district court's finding that one of skill in the art would not have chosen the structurally closest prior art compound... as the lead compound in light of other compounds with more favorable characteristics. [The Federal Circuit] reached the same result in *Eli Lilly*." *Daiichi* at 1353. In *Daiichi*, the Federal Circuit also rejected the use of "undisputedly the closest prior art" compound as a lead. Rather, "proving a reason to select a compound as a lead compound depends on more than just structural similarity, but also knowledge in the art of the functional properties and limitations of the prior art compounds." *Daiichi* at 1354. Indeed, "it is the possession of promising useful properties in a lead compound that motivates a chemist to make structurally similar compounds." *Daiichi* at 1354. In the present case, nothing in Himmelsbach would have provided one of ordinary skill in the art with any reason to select Example (38) as a lead because Himmelsbach did not disclose any activity, let alone functional properties, for Example (38).

Himmelsbach disclosed 16 synthetic examples and provides physical data for 166 different compounds made according to those synthetic procedures. Himmelsbach provided biological data for only 27 of those 166 compounds. Column 19, line 49 to column 20, line 15. However, Himmelsbach provides no biological or physical data for Example (38). Rather, Example (38) appears to be one of 186 prophetic compounds disclosed in the reference. The structures of those compounds are immediately preceded by classic prophetic language “[t]he following compounds may also be prepared analogously to the foregoing Examples and other methods known from the literature[.]” Column 56, lines 9 to 12. Instead, “[p]otent and promising activity in the prior art trumps mere structural relationships.” Daiichi at 1354 (emphasis added). Without any biological or even physical data, much less an indication of activity, one of ordinary skill in the art would not have had any reason to select Example (38) as a lead.

Additionally, Himmelsbach clearly discloses genres of “[p]articularly preferred compounds[,]” “[m]ost particularly preferred compounds” and further “[p]articularly preferred compounds” that do not encompass Example (38). Column 6, line 27 through column 12, line 12. Moreover, Himmelsbach provides a list of 22 specific “examples of particularly preferred compounds” that also does include Example (38). Column 12, line 32 through column 13, line 28. Given Himmelsbach’s narrowing focus on preferred genres and compounds that do not include Example (38), one of ordinary skill in the would have no reason to select Example (38) as a lead.

Accordingly, applicants respectfully submit that the ordinarily skilled artisan would have had no reason to select Example (38) as a lead and request the Examiner withdraw the rejection.

II. Motivation to Modify

Applicants respectfully submit that one of ordinary skill in the art would also not have been motivated to modify Example (38) to obtain the presently claimed compound.

The Office Action cites “R^b: column 1, lines 53-54; and R¹-R³: column 1, line 56 through column 2, line 3” of Himmelsbach for the proposition that the reference “discloses that p-fluoro and o-fluoro are alternatively usable on the anilino ring at C-4 of the quinazoline core[.]” Applicants respectfully disagree with this statement as the cited

passage does not make any reference to the ortho or para position of the phenyl ring. In fact, the cited passage makes no mention whatsoever regarding the specific position of any substituent on the phenyl ring. Instead, the cited passage merely provides that “the phenyl nucleus is substituted in each case by the groups R^1 to R^3 ” without specifying where on the phenyl ring any of numerous possible R^1 to R^3 groups is located. These numerous possible R^1 to R^3 substituents give rise to an even larger number of possible substitution patterns on the phenyl ring when considered in combination.

Himmelsbach’s mere listing of numerous possible substituents on a phenyl ring without any indication as to where any of those substituents should be located does not disclose “that p-fluoro and o-fluoro are alternatively usable” as stated in the Office Action, particularly absent hindsight. Moreover, Himmelsbach does not specifically disclose any compound or embodiment substituted at the ortho, or 2-position, of the phenyl ring.

Instead, Himmelsbach reveals an absolute preference for substitution at the 3-, 4-, or 3-,4- position(s) on the phenyl ring. All of Himmelsbach’s “[p]articularly preferred[.]” “[m]ost particularly preferred” and further “[p]articularly preferred” genres are only substituted at the 3-, 4-, or 3-,4- position(s) on the phenyl ring. Column 6, line 27 through column 12, line 12. Indeed, the phenyl groups in Himmelsbach’s further “[p]articularly preferred compounds” must either be 3-chloro, 4-fluoro disubstituted or 3-ethynyl substituted. Column 11, lines 8-12. Column 12, line 32 through column 13, line 28. Looking more broadly, all of the 166 exemplified compounds and all 186 of the apparently prophetic structures shown in columns 56-128 have 3-, 4-, or 3-,4- substitutions on the phenyl ring. Himmelsbach also discloses a strong preference for a 3-chloro, 4-fluoro disubstituted phenyl ring. All of the 22 specific “examples of particularly preferred compounds” are 3-chloro, 4-fluoro disubstituted. 144 of the 166 exemplified compounds (about 87%) are 3-chloro, 4-fluoro substituted, as are 171 of the 186 apparently prophetic structures (about 92%) shown in columns 56-128. In fact none, of the 352 specifically disclosed compounds has any substitution at the ortho, or 2-position.

Paraphrasing Daiichi, Himmelsbach “reveals a clear preference for [3-, 4-, or 3-,4-] groups [on the phenyl] ring. [All] of [Himmelsbach’s] compounds contain [3-, 4-, or 3-,4-] group[s]... as do [all] of the [26] compounds” for which data is given. Daiichi at 1355. Thus, 3-, 4-, or 3-,4- groups on the phenyl ring “are the essence of what the [Himmelsbach] patent teaches.” See Daiichi at 1355. “Altogether, [Himmelsbach’s] data and the structure of [the disclosed compounds] counter any notion that one of skill in the art would have been motivated to modify [the substitution pattern on the phenyl ring of Example (38)]. Such a [finding] would have been based on hindsight.” Daiichi at 1356.

The final Office Action attempted to support the obviousness rejection by twice making the statement that:

structural similarity between claimed and prior art subject matter, proved by combining references or otherwise, where the prior art gives reason or motivation to make the claimed compositions or compounds, creates a prima facie case of obviousness.

Here, neither the cited art nor the Office Action “gives reason or motivation to make the claimed ... compound[.]”

Additionally, the final Office Action first attempted to rebut applicants’ previous traversal of the rejection with the statement that

MPEP § 2144-I states that the rationale to modify or combine the prior art does not have to be expressly stated in the prior art; the rationale may be expressly or impliedly contained in the prior art or it may be reasoned from knowledge generally available to one of ordinary skill in the art, established scientific principles, or legal precedent established by prior case law. (emphasis in original)

The final Office Action appears to be using structural similarity as a *per se* rule for finding a *prima facie* case of obviousness without performing the requisite analysis discussed above. This is improper not only according to the case law but also according to the U.S.P.T.O.’s own updated examination guidelines recently published in the Federal Register. According to the U.S.P.T.O.’s Examination Guidelines,

[w]hen considering obviousness, Office personnel are cautioned against treating any line of reasoning as a *per se* rule... such rationales should not be treated as *per se* rules, but rather must be explained and shown to apply to the facts at hand... Simply stating the principle (e.g., ‘art recognized equivalent,’ ‘structural similarity’) without providing an explanation of its applicability to the facts of the case at hand is generally not sufficient to establish a *prima facie* case of obviousness.

Examination Guidelines Update: Developments in the Obviousness Inquiry After KSR v. Teleflex. Federal Register, Vol. 75, No. 169, 53643, 53645 (the “Examination Guidelines”).

The Examination Guidelines deal directly with the MPEP section cited above in the final Office Action stating that

[a]lthough the KSR approach is flexible with regard to the line of reasoning to be applied... “The Supreme Court in KSR noted that the analysis supporting a rejection under 35 U.S.C. 103 should be made explicit...” When setting forth a rejection, Office personnel are to continue to make appropriate findings of fact as explained in MPEP §§ 2141 and 2143, and must provide a reasoned explanation as to why the invention as claimed would have been obvious to a person of ordinary skill in the art at the time of the invention. This requirement for explanation remains even in situations in which Office personnel may properly rely on intangible realities such as common sense and ordinary ingenuity.

Examination Guidelines at 53645 (emphasis added). However, the final Office Action does not explicitly set forth any reasoned explanation for choosing Example (38) as a lead or for modifying the compounds in Himmelsbach to achieve the claimed compound.

The final Office Action further attempted to rebut applicants’ prior traversal when it stated

It is the examiner's position that the prior art of record lacks a *teach away* aspect. Applicant should further direct their attention to MPEP § 2141.02-VI which not only relates to references that may teach away, but also states that alternative embodiments should not be confused with *teaching away*, citing *In re Fulton* at 73 USPQ2d 1141: *The prior art's mere disclosure of more than one alternative does not constitute a teaching away from any of these alternatives because such disclosure does not criticize, discredit, or otherwise discourage the solution claimed in the '198 application. Indeed, in the case cited by appellants, In re Gurley, we held that the invention claimed in the patent application was unpatentable based primarily on a prior art reference that disclosed two alternatives, one of which was the claimed alternative. Accordingly, mere disclosure of alternative designs does not teach away.* (emphasis in original)

Regarding a teach away aspect, applicants have discussed the preferences in Himmelsbach in detail above. However, “even crediting [an] argument that the [Himmelsbach] patent does not each away from a [substitution at the 2-position of the phenyl ring], the [Himmelsbach] patent simply does not provide a reason to make such a modification.” Daiichi at 1358.

Accordingly, applicants submit that the claims are not rendered obvious over the cited references, and respectfully request the Examiner withdraw this rejection.

CONCLUSION

In view of the above remarks, applicants respectfully submit that this application is in condition for allowance and earnestly solicit notice to that effect. The Examiner is invited to contact the undersigned at the telephone number provided below if the Examiner believes such would be helpful in advancing the application to issue.

Respectfully submitted,

Dated: February 1, 2011

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